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Cost-of-illness of inflammatory bowel disease patients treated with anti-tumour necrosis factor: A French large single-centre experience

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Abstract

Background: No study has evaluated the direct annual costs of inflammatory bowel disease patients treated with anti-tumour necrosis factor therapy.

Objectives: The purpose of this study was to identify annual direct costs and main cost drivers of anti-tumour necrosis factor-treated inflammatory bowel disease patients.

Methods: All inflammatory bowel disease patients treated with infliximab or adalimumab at Nancy University Hospital were consecutively screened for inclusion from November 2016–February 2017. Data about hospitalisation, surgery, medication, outpatient visits, investigations and transport over the previous 12 months were retrospectively collected.

Results: A total of 108 patients ($n = 83$ Crohn's disease; $n = 25$ ulcerative colitis) were included. The mean annual cost per patient was €15,775 (standard deviation €7221), with no difference between Crohn's disease and ulcerative colitis ($p = 0.2$). The main cost driver was medication, which accounted for 84% of the total direct cost. Hospitalisation and surgery represented 11% and 2% of the direct costs. History of switch to another anti-tumour necrosis factor treatment was identified as the only independent predictor of greater direct costs in the multivariate analysis ($p = 0.0018$).

Conclusions: In a French tertiary referral centre, direct costs of anti-tumour necrosis factor therapy-treated patients were mainly driven by medication, while hospitalisation and surgery represented only a minor part of the costs. There was no difference between Crohn's disease and ulcerative colitis patients.

Keywords

Anti-tumour necrosis factor therapy, costs, Crohn's disease, inflammatory bowel disease, pharmacoeconomics, ulcerative colitis

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Key summary

Established knowledge

- The overall direct cost of inflammatory bowel disease (IBD) patients was historically driven by surgery and hospitalisation.
- Most cost-of-illness studies in IBD were performed before the introduction of biological therapies and can therefore be considered outdated.
- No study has evaluated the direct annual costs of IBD patients treated with anti-tumour necrosis factor (anti-TNF) therapy.

Significant new findings

- The mean annual cost per anti-TNF-treated IBD patient was €15,775, with no difference between Crohn's disease (CD) and ulcerative colitis (UC).
- Direct costs of anti-TNF-treated IBD patients were mainly driven by medication (84%), while hospitalisation (11%) and surgery (2%) represented only a minor part of the costs.
- History of switch to another anti-TNF treatment was identified as the only independent predictor of greater direct costs.
- Medication remains the pre-dominant cost driver in anti-TNF-treated IBD patients, even after the implementation of biosimilars.

Introduction

Inflammatory bowel diseases (IBDs), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic and disabling conditions.[1,2] As these diseases are not curable, and often require long-life treatment, their economic impact is of interest given the importance of health-care costs and growing constraints on health-care budgets.

The overall direct cost of IBD patients was historically driven by surgery and hospitalisation.[4–6] The advent of anti-tumour necrosis factor (anti-TNF) therapy has drastically changed the treatment of IBD patients over the past two decades.[7] Infliximab and adalimumab are approved for both CD and UC.[8,9] Certolizumab is not approved in France while golimumab is approved only for UC.[10,11] A recent analysis of the French administrative databases estimated the probability of anti-TNF exposure five years after diagnosis to 33.8% in CD and 12.9% in UC.[12] Most cost-of-illness studies in IBD were performed before the introduction of these expensive biological therapies and can therefore be considered outdated.[4,13–15]

The recent 'Cost of inflammatory Bowel Disease in The Netherlands' (COIN) study has shown that IBD health-care costs are now mainly driven by medication, most importantly by anti-TNF therapy. Hospitalisation and surgery accounted only for a minor part of expenses.[3] While direct costs, such as medication use, diagnostic procedures, hospitalisation and indirect cost were analysed in this study, the examined period was limited to three months and some costs, such as transportation use and the need for a nurse for the injections of subcutaneously administered medication, were not taken into account. Furthermore, differences in the health-care systems between The Netherlands and France make data from the COIN study difficult to extrapolate.

Although adalimumab is administered subcutaneously, infliximab infusion requires repeated hospitalisations and patients spend a median time of 6.5 h outside their home for each perfusion. This represents an extra burden for infliximab-treated patients and for the health-care system.[16]

At present, no cost-of-illness study has examined the cost of IBD patients treated with infliximab or adalimumab. Therefore, the present study was initiated in order to estimate the direct costs of IBD patients under anti-TNF therapy and to determine their main cost drivers.

Materials and methods

This study was designed to identify medical and non-medical direct costs of patients treated with infliximab or adalimumab for CD or UC during a period of one year.

Patient selection

All IBD patients that were hospitalised or attended the outpatient clinic at the Nancy University hospital (CHRU Nancy), France, were consecutively screened for eligibility between November 2016–February 2017. Two groups were identified: infliximab-treated and adalimumab-treated patients. The number of patients needed in each treatment group was estimated as at least 50 to obtain reasonable precision of cost estimates.

Inclusion criteria were: (a) established diagnosis of CD or UC; (b) age 18 years or more at the time of

inclusion; (c) at least one infusion of infliximab or one injection of adalimumab within the past 12 months. Exclusion criteria were: (a) patients refusing or unable to fill in the questionnaire; (b) patients who did not receive at least one administration of infliximab or adalimumab in the year before inclusion.

Data collection

Information concerning disease and patients' characteristics was collected from electronic medical records in the year preceding the inclusion. This information withheld the type of IBD, disease location and disease behaviour (Montréal classification), age, gender, body mass index, family history of bowel disease, past abdominal surgery and data concerning medical consumption (drug consumption, visits at consultation and ambulatory care, hospitalisation, surgery, diagnosis, monitoring investigations and biologics history). In addition, a clinical research assistant together with the patient administered a questionnaire with five questions at the day of inclusion, requesting general information and data about health consumption that were not readily available in the electronic medical records (Supplementary Material Table 1).

Cost valuation

All consumptions for various expense items were valued in monetary units (euros) from the National Health Insurance System (NHIS) perspective in 2018. Concerning medication cost, valuation was based on price observed during data collection from November 2016–February 2017. All available information on 'Diagnosis-Related Group' (DRG) for each patient's in-hospital stay was retrieved from the 'medicalised information system program' (PMSI) database. DRG is a fixed fare paid by the NHIS to hospitals in return for procedures and in-hospital stay. Ambulatory care, including general practitioner and specialist visits, nurse care, care management coordination, therapeutic education and transport costs were valued according to the 'Nomenclature Générale des Actes Professionnels' (NGAP), which serves as a basis for NHIS to reimburse all ambulatory care including transportation expenses.

To account for a recent decrease of cost of biologics in France due to the advent of infliximab biosimilars, overall costs in 2018 were also calculated assuming that the prescription practices were similar to those observed in the study period.

Statistical analysis

The descriptive analysis of socio-demographic, clinical, and care consumption variables used mean and standard deviation (SD) for quantitative variables and percentages for qualitative variables. Quantitative variables were categorised where appropriate. Annual costs for each consumption unit were calculated as the weighted sum of unit costs and described by mean, SD, median and interquartile range (IQR).

Factors associated with cost outcomes were analysed in a multivariate linear regression model, using variables below 0.2 p-value significance in univariate analysis. Age and gender, considered as adjustment variables, were included in the multivariate model regardless of the level of significance. The final model retained all variables significant at 0.05 alpha levels.

All analysis were conducted using SAS Enterprise Guide - version 7.13 (SAS Institute Inc., Cary, North Carolina, USA).

Ethical consideration

The study received approval from the Institutional review board Commission Nationale Informatique et Liberté (CNIL; R2016-43; 25 November 2016). Written, informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Results

Study population

A total of 108 patients (83 CD and 25 UC) were included in the study over a period of four months. Table 1 presents the demographic and disease characteristics of the study population. A total of 42 (39%) patients had previous intestinal surgery. The mean disease duration at time of inclusion was 10.7 years (SD 7.9 years). The mean anti-TNF exposure duration for the year preceding inclusion was 338 days (SD 75 days).

Health-care costs

The study was performed in 2016 and 2017. The global health-care resource utilisation and annual costs at that period are shown in Table 2, while Supplementary Material Table 2 represents the different parameters collected, together with their corresponding prices. The mean and median annual health-care costs per patient were €15,775 (SD €7221) and €12,915 (IQR €10,732), respectively. The total mean cost of UC (€17,376, SD €7592) was numerically higher than the total mean cost of CD (€15,292, SD €7369), but this difference was not statistically significant ($p = 0.2$).

Table 1. Demographic and disease characteristics of the study participants (n = 108).

	n	(%)/mean	SD
Gender			
Male	61	(56)	
Female	47	(44)	
Age (years)		37.6	12.8
Smoking			
Current	23	(21)	
Never	59	(55)	
Ex-smoker	26	(24)	
Disease duration (years)		10.7	7.9
Type of IBD			
CD	83	(77)	
UC	25	(23)	
Montreal extent-CD			
Small bowel - L1	21	(25)	
Large bowel - L2	12	(14)	
Small and large bowel - L3	47	(57)	
Upper - L4	3	(4)	
Montreal behaviour-CD			
Non-penetrating non-stricturing - B1	34	(41)	
Stricturing - B2	21	(25)	
Penetrating - B3	28	(34)	
Perianal disease	33	(40)	
Disease localisation-UC			
Limited to the rectum - E1	3	(12)	
Left-sided UC - E2	5	(20)	
Extensive UC - E3	17	(68)	
Weight (kg)[a]		70.8	14.7
Height (cm)[b]		170.5	11.5
Distance residence-hospital (km)		62.5	48.2
Family history of IBD	11	(10)	
Previous abdominal surgery	42	(39)	

CD: Crohn's disease; IBD: inflammatory bowel disease; SD: standard deviation; UC: ulcerative colitis.
[a]Data could not be found for two patients; [b]data could not be found for nine patients.

Drivers of health-care costs

Medication was the major driver of health-care costs, with a mean of €13,172 (IQR €9360) (84%), while hospitalisation and surgery, respectively, accounted for 11% and 2% of the direct costs. Humira (adalimumab) represented a mean cost per patient of €14,058 (SD €6734), while Remicade (infliximab originator) represented a mean cost per patient of €12,347 (SD €6738), and Inflectra (infliximab biosimilar) represented a mean cost per patient of €4644 (SD €2315).

Table 2. Health-care resource utilisation and annual cost (in €).

	%	*n*	Mean	Median	Q1	Q3
Total		108	15,775	12,915	11,299	22,031
Hospitalisation	11%					
Day hospital	8%	66	2095	2343	1674	2343
Full hospitalisation	3%	16	2963	1658	827	4519
Biologicals	84%	108	6534	4688	430	10,140
Remicade		50	12,347	10,530	8190	14,040
Inflectra		9	4644	3300	3300	6875
Humira		54	14,058	11,599	11,599	22,769
Investigations	1%	83	142	127	69	154
Surgery	2%	7	4972	4393	878	9943
Consultation	1%	96	101	84	56	112
Transport	2%	94	415	138	37	482

In multivariate linear regression analysis, and after adjustment for age and gender, the only variable associated with a greater cost of IBD was a history of a switch from one anti-TNF agent to another ($p = 0.0018$; Supplementary Material Table 3). Regression analyses were also performed in infliximab-treated and adalimumab-treated patient separately, with no differences between both.

Health-care costs in the era of biosimilars (2018–2019)

The advent of biosimilars, introduced in France in 2015 with increasing uptake ever since, induced a decrease in cost of biologics since 2018, and the cost of the infliximab biosimilar and infliximab originator became equivalent. Taken into account this price switch, we estimated that the mean cost in 2018 per year and per patient would have been €10,658 (SD €6118), and that biologics accounted for 75% of direct costs (data not shown).

Discussion

To the best of our knowledge, the present study is the first to analyse the cost-of-illness of IBD patients treated with biologic therapy (infliximab or adalimumab). This specific population is of major interest as it is known to be the one with the most severe disease phenotypes, with long treatment duration and a high risk of disease complications, and thus with a high economic burden for the health-care system. We found that anti-TNF therapy represented the main part (84%) of the cost, whereas hospitalisation accounted for 11% and surgery for only 2% of direct costs. This contrasts with data from the pre-biologics era, where surgery was found to be the main driver of health-care

costs in IBD patients.[4,14] Our results are in line with those of the COIN study, which found that medication cost accounted for up to 71% in CD and 59% in UC while hospitalisation and surgery accounted for 19% and <1%, respectively.[3] This study evaluated the global cost of a general population of IBD patients in several Dutch hospitals, and anti-TNF treated patients accounted for only 15% of the global population of this study.

The present study provides unique information on the one-year global cost of an anti-TNF-treated patient, with a mean rate of €15,775 per year, and a maximum of €41,937 per year. An American study conducted in 2004 included more than 9000 patients and found a mean cost of 8265 US dollars for CD and 5066 US dollars for UC, which is equivalent to €7748 and €4752, respectively, using the currency rate of 2016.[17]

Only a history of switch to another anti-TNF treatment was identified as a predictor of direct costs in the multivariate analysis In 2004, Bassi et al. found disease severity to be predictive of a greater six-month cost.[14] Non-responder patients or patients with loss of response to anti-TNF often need a switch of biotherapy and are known to have lower rate of response for treatment. Therefore, these patients frequently have treatment adaptations, such as higher dosage or frequency, which can indeed explain a greater cost.

For CD and UC, global mean costs were €15,292 and €17,376, respectively, and no significant difference was found between both. Previous reports showed that costs related to CD management were greater than costs related to UC.[3,4,14,17,18] However, the proportion of anti-TNF treated patients was much higher in patients with CD compared with patients with UC, and this likely explains the difference observed in these studies.

The strengths of this study reside in the studied period of 12 months and in the comprehensive data collection from electronic medical records, which was completed by an additional questionnaire. Of note, no patient refused to fill in the questionnaire. This method ensured robust data and very few omission biases. We confirm the data from the COIN trial in a different country (and health-care setting) than the Netherlands. Additionally, we added an estimate of the costs after the advent of biosimilars. We also recognise several limitations. Indirect costs due to productivity losses from work absence and short-term disability were not assessed. We did not report the cost of other drugs such as azathioprine and methotrexate. Thirty-two percent of our patients received one of these treatments in the year preceding inclusion, but we considered their cost to be negligible since the cost of one year of azathioprine treatment (100 mg per day) is estimated to be €167, and one year of oral methotrexate (15 mg per week) is estimated to be €82. Due to health-care system differences, our results are difficult to extrapolate to other countries, but it may help us to understand the global trend in the biologics era. Several studies showed that therapeutic drug monitoring can improve cost-effectiveness of anti-TNF therapy.[19–21] The specific benefit of such an approach could not be taken into account in our single-centre study, since all included patients were treated according to this principle and a control cohort was lacking. It is noteworthy that other biologics are now available for IBD patients in France, but our study was conducted before the reimbursement of vedolizumab and ustekinumab.

Infliximab biosimilar (Flixabi, Inflectra or Remsima) was first used in France in 2015. Our study took place between November 2016–February 2017, when the implementation of biosimilars only began enrolment in our centre. This is the reason why only nine patients of the studied population were treated with an infliximab biosimilar. Major decreases in both prices of the infliximab originator and biosimilars occurred thereafter. The global direct cost may therefore be different nowadays. When taking into account this price switch, we found that the advent of biosimilars indeed relieved a part of the burden of drug costs, but that drug treatment continued to be the major cost driver. Adalimumab biosimilars arrived in Europe at the end of 2018 with prices 45% lower compared to Humira (adalimumab originator), and this will further decrease the global costs of anti-TNF treated patients.

In conclusion, our study is the first to evaluate the mean annual direct cost of IBD patients treated with anti-TNF therapy in France, estimating a mean global cost of €15,775 per patient. Medication cost represented more than 80% of this total cost, whereas hospitalisation and surgery represented only a minor part. To ensure a diminution of global direct cost of IBD patients, efforts should be made mainly on reducing the price of biologics, as recently initiated in France and other countries across Europe with the implementation of biosimilars. However anti-TNF therapy likely contributed to a reduction of the global surgery rate in IBD, cost-effectiveness studies comparing different approaches such as early surgery versus prolonged medical treatment (including switching to second- and third line biologicals), are still needed, especially in CD. Similar research to the study presented here should be conducted in the rest of the world to better identify health-care costs related to the management of IBD patients in different and specific regional settings.

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Declaration of conflicting interests

LP received travel fees from AbbVie, Ferring and Takeda. LPB received honoraria from Merck, AbbVie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, HAC-Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis. The other authors have nothing to disclose.

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Ethics approval

The study received approval from the Institutional review board Commission Nationale Informatique et Liberté (CNIL; R2016-43; 25 November 2016). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Informed consent

Written, informed consent was obtained from each patient included in the study.

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